Refine Search

Search Results -

Terms	Documents
L1 and diagnostic	2

Database: US Pre-Grant Publication Full-Text Database; US Patents Full-Text Database; US OCR Full-Text Database; EPO Abstracts Database; JPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L7

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Wednesday, March 14, 2007 Purge Queries | Printable Copy | Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L7	l1 and diagnostic	2	L7
L6	L5 and label$ near5 (TCR$ or T near cell near receptor$)	10	L6
L5	muta$ near5 (TCR$ or T near cell near receptor$) near5 high$ near5 affinit$	13	L5
L4	muta$ near5 (TCR$ or T near cell near receptor$)	463	L4
L3	L1 and dissociation near3 constant$	1	L3
L2	L1 and high near affinit$	2	L2
L1	20040146952	2	L1

END OF SEARCH HISTORY

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Processed  20 of  41 files ...
Completed processing all files
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        13756133  T
        20698929  CELL
         7521126  RECEPTOR?
          224362  T(N)CELL(N)RECEPTOR?
               0  LIGAND$
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          224362  T(N)CELL(N)RECEPTOR?
         1969093  LIGAND?
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          224375  T(N)CELL(N)RECEPTOR?
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                  RECEPTOR?)
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        20498408  INCREAS?
         5189144  ENHANCE?
         1779036  AFFINIT?
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      Display 6/9/1     (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.

10954672   PMID: 8757301
  Two distinct stimulus-dependent pathways lead to production of soluble
murine interleukin-4 receptor.
  Blum H; Wolf M; Enssle K; Rollinghoff M; Gessner A
  Institute of Clinical Microbiology and Immunology, University of
Erlangen-Nurnberg, Germany.
  Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES)  Sep 1
1996, 157 (5) p1846-53, ISSN 0022-1767--Print  Journal Code: 2985117R
  Publishing Model Print
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: MEDLINE; Completed
  Subfile:  AIM; INDEX MEDICUS
  The IL-4R exists in two forms, either membrane bound or as a soluble (s)
molecule. Since the sIL-4R binds to its  ***ligand***  with  ***high***

                                    -more-
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      Display 6/9/1     (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 2007 Dialog. All rts. reserv.
affinity , thereby acting as an immunoregulatory molecule, we were
interested in the processes leading to its release. First, the release of
sIL-4R in the model of murine leishmaniosis was analyzed. Infection of mice
with Leishmania major resulted in up-regulation of sIL-4R production by
Ag-stimulated CD4+ T cells, with a maximum around 7 days after infection.
To clarify the mechanisms underlying sIL-4R release, in vitro studies were
performed. After stimulation of naive lymphoid cells with IL-4, sIL-4R
release was dependent on up-regulation of spliced IL-4R mRNA, as shown by
inhibition with specific antisense oligonucleotides. In contrast to this,
no increase in the spliced IL-4R mRNA and no inhibitory influence of
antisense oligonucleotides were observed after stimulation of T cells from
IL-4-deficient mice with anti-CD3 mAb. Thus,  ***TCR***  stimulation can lead
to IL-4-independent sIL-4R production. Under these conditions proteolytic
shedding of membrane-bound IL-4R appears to be the principal mechanism of
release, since in contrast to stimulation with IL-4, iodinated sIL-4R could
only be immunoprecipitated after cell surface labeling and subsequent
  ***TCR***  stimulation. The common gamma-chain, a component of the IL-4R

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Display 6/9/1 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
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complex, did not appear to be involved in the pathways leading to sIL-4R expression. This analysis suggests the existence of two differentially regulated pathways of sIL-4R release, possibly having different consequences for the regulation of IL-4 bioactivity.
Tags: Female
Descriptors: *Antigens, CD--biosynthesis--BI; *Antigens, CD--immunology --IM; *Interleukin-4--metabolism--ME; *Lymphocyte Activation; *Receptors, Interleukin--biosynthesis--BI; *Receptors, Interleukin--immunology--IM; Alternative Splicing--immunology--IM; Animals; Antigens, CD--metabolism--ME ; Interleukin-4--physiology--PH; Leishmaniasis, Cutaneous--immunology--IM; Mice; Mice, Inbred BALB C; Mice, Inbred C3H; Mice, Inbred C57BL; Mice, Inbred CBA; Mice, Inbred DBA; Mice, SCID; RNA, Messenger--biosynthesis--BI; Receptors, Interleukin--metabolism--ME; Receptors, Interleukin-4; Research Support, Non-U.S. Gov't; Solubility; T-Lymphocytes--immunology--IM; T-Lymphocytes--metabolism--ME
CAS Registry No.: 0 (Antigens, CD); 0 (RNA, Messenger); 0 (Receptors, Interleukin); 0 (Receptors, Interleukin-4); 207137-56-2

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Display 6/9/1 (Item 1 from file: 154)
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(c) format only 2007 Dialog. All rts. reserv.
(Interleukin-4)
Record Date Created: 19961122
Record Date Completed: 19961122

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Display 6/9/2 (Item 1 from file: 370)
DIALOG(R)File 370:Science
(c) 1999 AAAS. All rts. reserv.

00505223 (THIS IS THE FULLTEXT)
Structural Basis of Plasticity in T Cell Receptor Recognition of a Self Peptide-MHC Antigen
Garcia, K. Christopher; Degano, Massimo; Pease, Larry R.; Huang, Mingdong; Peterson, Per A.; Teyton, Luc; Wilson, Ian A.
K. C. Garcia, M. Degano, M. Huang, and I. A. Wilson are in the Department of Molecular Biology and the Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. L. R. Pease is in the Department of Immunology, Mayo Clinic, Rochester, MN 55905, USA. P. A. Peterson is at the R. W. Johnson Pharmaceutical Research Institute-La Jolla, 3535 General Atomic Court, San Diego, CA 92121, USA. L. Teyton is in the Department of Immunology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.
Science Vol. 279 5354 pp. 1166
Publication Date: 2-20-1998 (980220) Publication Year: 1998

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Display 6/9/2 (Item 1 from file: 370)
DIALOG(R)File 370:Science
(c) 1999 AAAS. All rts. reserv.
Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: Research Articles
Word Count: 5152

Abstract: The T cell receptor (TCR) inherently

has dual specificity. T cells must recognize self-antigens in the thymus during maturation and then discriminate between foreign pathogens in the periphery. A molecular basis for this cross-reactivity is elucidated by the crystal structure of the alloreactive 2C TCR bound to self peptide-major histocompatibility complex (pMHC) antigen H-2K.sup(b)-dEV8 refined against anisotropic 3.0 angstrom resolution x-ray data. The interface between peptide and TCR exhibits extremely poor shape complementarity, and the TCR (beta) chain complementarity-determining region 3 (CDR3) has minimal interaction with the dEV8 peptide. Large conformational changes in three of the ***TCR*** CDR loops are induced upon binding, providing a mechanism of structural

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Display 6/9/2 (Item 1 from file: 370)
DIALOG(R)File 370:Science
(c) 1999 AAAS. All rts. reserv.
plasticity to accommodate a variety of different peptide antigens. Extensive TCR interaction with the pMHC a helices suggests a generalized orientation that is mediated by the V.inf(a) domain of the TCR and rationalizes how TCRs can effectively "scan" different peptides bound within a large, low-affinity MHC structural framework for those that provide the slight additional kinetic stabilization required for signaling.

Text: The phenomenon of MHC restriction is the basis of the cell-mediated immune response to foreign pathogens (B1) . The central molecular event governing this process is the engagement of the clonotypic a (beta) TCR by particular MHC class I or class II molecules in association with processed peptides (B2) . Upon engagement of the pMHC, a proliferative signal is transduced into the T cell by subsequent activation of the nonclonotypic members of the TCR signaling complex: CD8 (class I) or CD4 (class II), and CD3 (gamma) , (delta) , epsilon , and (zeta)

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Display 6/9/2 (Item 1 from file: 370)
DIALOG(R)File 370:Science
(c) 1999 AAAS. All rts. reserv.
(B3) (B4) .

It has become clear that a structural plasticity, or flexibility, in recognition of pMHC (B5) (B6) and a biological plasticity in response to ligand (B3) (B4) (B7) (B8) (B9) are essential properties for the survival and function of T cells. Thymic development of T cells depends on weak interactions with self pMHC ***ligands*** (B10) . T cells selected for maturation then exhibit high frequencies of alloreactivity, or cross-reactivity, against both self and foreign pMHC complexes in the periphery (B11) . This ***TCR*** cross-reactivity can manifest itself in a range of different biological outcomes, depending on the pMHC ligand (B5) (B6) (B7) (B8) , and includes agonist and antagonist effects (B8) , which have been correlated to the half-life of the TCR-pMHC complex and co-receptor association (B12) . An important question is whether there are structural properties unique to the TCR-pMHC interface that facilitate this broadened specificity.

T cell receptor structure determinations have illuminated similarities and differences with antibodies and how the

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Display 6/9/2 (Item 1 from file: 370)
DIALOG(R)File 370:Science
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TCR may be particularly suited to bind pMHC (B13) (B14) (B15) (B16) .

The orientation of the TCR to the pMHC has been determined for two TCR-pMHC complexes (B15) (B16) , one of which represents a refined structure at 2.6 angstrom (B16) . The overall topology of these complexes could be reconciled with earlier predictions inferred from biological data (B17) (B18) (B19) .

We have focused our efforts on the murine 2C TCR system (B20) (B21) , which is the only a (beta) TCR for which distinct self (H-2K.sup(b)-dEV8) (B6) and foreign [H-2K.sup(bm3)-dEV8 (B6) and H-2L.sup(d)-p2Ca (B22)] ***ligands*** have been defined (B23) . Thymocytes of 2C transgenic mice are positively selected in the presence of H-2K.sup(b) and negatively selected in the presence of the allo- ***ligands*** H-2K.sup(bm3) (a naturally occurring, two-amino acid mutant of H-2K.sup(b)) or H-2L.sup(d) (B21) . dEV8 is a murine self-peptide, derived from intracellular processing of the murine mitochondrial respiratory protein complex (MLRQ), that was eluted from H-2K.sup(b)-and H-2K.sup(bm3)-bearing cells (B6) . When bound to H-2K.sup(b), dEV8 is a

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Display 6/9/2 (Item 1 from file: 370)

weak agonist for the 2C cytotoxic T cell but a strong agonist for the 2C allo- ***ligand*** H-2K.sup(bm3). Therefore, dEV8 may be one of a number of peptides bound to H-2K.sup(b) that is capable of selecting 2C thymocytes (B6) . A crystal structure of 2C in complex with H-2K.sup(b)-dEV8 can allow us to explain how just two amino acid changes are sufficient to convert H-2K.sup(b) into an alloreactive ***ligand*** (B21) .

We report here the refined crystal structure of the mouse 2C TCR in complex with mouse MHC class I H-2K.sup(b) bound to the self-peptide dEV8 (EQYKFYSV) (B24) . We also briefly describe the 2.3 angstrom structure of H-2K.sup(b)-dEV8, which, along with the unliganded 2.5 angstrom structure of the 2C TCR (B15) , allows us to assess whether there are structural alterations in either the TCR or pMHC upon complexation. We can now more clearly explain the degenerate specificity of TCR-pMHC interaction in terms of a structural plasticity in the ***TCR*** -pMHC interface. The ability to alter the shape of the ***TCR*** combining site through deformation of the peptide-contacting complementarity-determining region (CDR) loops and their side chain

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Display 6/9/2 (Item 1 from file: 370)

orientations, along with large unfilled spaces in the interface, permits useful accommodation of different ***ligands*** . This in turn gives rise to the biological and functional plasticity that is based on varying affinities and stabilities observed in most TCR systems in the in vivo signal transduction events.

Overall structure. The 2C ***TCR*** and H-2K.sup(b)-dEV8 were expressed and purified from Drosophila melanogaster cells and cocrystallized (B23) . The structure was determined by molecular replacement and refined with the use of multidomain real-space averaging and torsion angle dynamics (B25) (Table 1). The diffraction of these crystals is markedly anisotropic along the b* direction, thus limiting the effective resolution of the refined structure (maximum resolution along a* and c* is beyond 3.0 angstrom , but only ~4.2 angstrom along b*). Despite the presence of this anisotropic decay, all of the domains of the two TCR-pMHC complexes in the asymmetric unit are ordered (B26) , with the highest quality electron density being in the TCR-pMHC interfaces. The relation of the two molecules in the asymmetric unit (B27)

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      Display 6/9/2     (Item 1 from file: 370)
DIALOG(R)File 370:Science
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does not support other crystallographically derived dimerization models for
  ***TCR***  -pMHC complexes (B28) .
     The overall relative orientations of the TCR and pMHC in the
refined 2C-H-2K.sup(b)-dEV8 complex are identical to those derived from the
original molecular replacement solution (B15) . The   ***TCR***   crosses the
pMHC in an approximate diagonal orientation, in which the TCR a chain
lies over the bound peptide NH.inf(2)-terminal residues and the  (beta)
chain covers the peptide COOH-terminal residues (Figs. 1 and 2). Given the
steric limitations that the MHC helices place on the depth of the approach
of the TCR to the bound peptide, the diagonal orientation allows for
the deepest docking solution of the   ***TCR***   CDRs onto the pMHC surface.
The unusual noncanonical fold of the   ***TCR***   C.inf(a) domain (B15)  is
confirmed in each of the two complexes.
     The   ***TCR***  -pMHC interface. About 1876  angstrom .sup(2) of surface
is buried in the 2C-K.sup(b) interface, of which 900  angstrom .sup(2) is
contributed by the   ***TCR***   and 976  angstrom .sup(2) by the pMHC (B25) .
Within the pMHC composite surface, about 222  angstrom .sup(2), or 23% of

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        20498408  INCREAS?
         5189144  ENHANCE?
         1779036  AFFINIT?
          189914  TCR?
        13756133  T
        20698929  CELL
         7521126  RECEPTOR?
          224362  T(N)CELL(N)RECEPTOR?
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                  OR T (N) CELL (N) RECEPTOR?)
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Processed  20 of  41 files ...
Completed processing all files
            2197  S7
         2615450  LABEL?
          475533  TAG?
          189914  TCR?
        13756133  T
        20698929  CELL
         7521126  RECEPTOR?
          224375  T(N)CELL(N)RECEPTOR?
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S9 1 S8 NOT PY>2000
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DIALOG(R)File 370:Science

00505223 (THIS IS THE FULLTEXT)
Structural Basis of Plasticity in T Cell Receptor Recognition of a Self Peptide-MHC Antigen
Garcia, K. Christopher; Degano, Massimo; Pease, Larry R.; Huang, Mingdong; Peterson, Per A.; Teyton, Luc; Wilson, Ian A.
K. C. Garcia, M. Degano, M. Huang, and I. A. Wilson are in the Department of Molecular Biology and the Skaggs Institute of Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA. L. R. Pease is in the Department of Immunology, Mayo Clinic, Rochester, MN 55905, USA. P. A. Peterson is at the R. W. Johnson Pharmaceutical Research Institute-La Jolla, 3535 General Atomic Court, San Diego, CA 92121, USA. L. Teyton is in the Department of Immunology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.
Science Vol. 279 5354 pp. 1166
Publication Date: 2-20-1998 (980220) Publication Year: 1998

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Display 9/9/1 (Item 1 from file: 370)
DIALOG(R)File 370:Science

Document Type: Journal ISSN: 0036-8075
Language: English
Section Heading: Research Articles
Word Count: 5152

Abstract: The T cell receptor (TCR) inherently has dual specificity. T cells must recognize self-antigens in the thymus during maturation and then discriminate between foreign pathogens in the periphery. A molecular basis for this cross-reactivity is elucidated by the crystal structure of the alloreactive 2C TCR bound to self peptide-major histocompatibility complex (pMHC) antigen H-2K.sup(b)-dEV8 refined against anisotropic 3.0 angstrom resolution x-ray data. The interface between peptide and TCR exhibits extremely poor shape complementarity, and the TCR (beta) chain complementarity-determining region 3 (CDR3) has minimal interaction with the dEV8 peptide. Large conformational changes in three of the TCR CDR loops are induced upon binding, providing a mechanism of structural plasticity to accommodate a variety of different peptide antigens.

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DIALOG(R)File 370:Science

Extensive TCR interaction with the pMHC a helices suggests a generalized orientation that is mediated by the V.inf(a) domain of the TCR and rationalizes how TCRs can effectively "scan" different peptides bound within a large, low-affinity MHC structural framework for those that

provide the slight additional kinetic stabilization required for signaling.

Text: The phenomenon of MHC restriction is the basis of the cell-mediated immune response to foreign pathogens (B1) . The central molecular event governing this process is the engagement of the clonotypic a (beta) TCR by particular MHC class I or class II molecules in association with processed peptides (B2) . Upon engagement of the pMHC, a proliferative signal is transduced into the T cell by subsequent activation of the nonclonotypic members of the TCR signaling complex: CD8 (class I) or CD4 (class II), and CD3 (gamma) , (delta) , epsilon , and (zeta) (B3) (B4) .

It has become clear that a structural plasticity, or flexibility, in

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Display 9/9/1 (Item 1 from file: 370)
DIALOG(R)File 370:Science

recognition of pMHC (B5) (B6) and a biological plasticity in response to ligand (B3) (B4) (B7) (B8) (B9) are essential properties for the survival and function of T cells. Thymic development of T cells depends on weak interactions with self pMHC ligands (B10) . T cells selected for maturation then exhibit high frequencies of alloreactivity, or cross-reactivity, against both self and foreign pMHC complexes in the periphery (B11) . This TCR cross-reactivity can manifest itself in a range of different biological outcomes, depending on the pMHC ligand (B5) (B6) (B7) (B8) , and includes agonist and antagonist effects (B8) ; which have been correlated to the half-life of the TCR-pMHC complex and co-receptor association (B12) . An important question is whether there are structural properties unique to the TCR-pMHC interface that facilitate this broadened specificity.

T cell receptor structure determinations have illuminated similarities and differences with antibodies and how the TCR may be particularly suited to bind pMHC (B13) (B14) (B15) (B16) . The orientation of the TCR to the pMHC has been determined for two TCR-pMHC complexes (B15) (B16) , one of which represents a refined structure at 2.6 angstrom (B16) . The overall

-more-

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Display 9/9/1 (Item 1 from file: 370)
DIALOG(R)File 370:Science

topology of these complexes could be reconciled with earlier predictions inferred from biological data (B17) (B18) (B19) .

We have focused our efforts on the murine 2C TCR system (B20) (B21) , which is the only a (beta) TCR for which distinct self (H-2K.sup(b)-dEV8) (B6) and foreign [H-2K.sup(bm3)-dEV8 (B6) and H-2L.sup(d)-p2Ca (B22)] ligands have been defined (B23) . Thymocytes of 2C transgenic mice are positively selected in the presence of H-2K.sup(b) and negatively selected in the presence of the allo-ligands H-2K.sup(bm3) (a naturally occurring, two-amino acid mutant of H-2K.sup(b)) or H-2L.sup(d) (B21) . dEV8 is a murine self-peptide, derived from intracellular processing of the murine mitochondrial respiratory protein complex (MLRQ), that was eluted from H-2K.sup(b)-and H-2K.sup(bm3)-bearing cells (B6) . When bound to H-2K.sup(b), dEV8 is a weak agonist for the 2C cytotoxic T cell but a strong agonist for the 2C allo-ligand H-2K.sup(bm3). Therefore, dEV8 may be one of a number of peptides bound to H-2K.sup(b) that is capable of selecting 2C thymocytes (B6) . A crystal structure of 2C in complex with H-2K.sup(b)-dEV8 can allow us to explain how just two amino acid changes

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DIALOG(R)File 370:Science

are sufficient to convert H-2K.sup(b) into an alloreactive ligand (B21) .

We report here the refined crystal structure of the mouse 2C TCR in complex with mouse MHC class I H-2K.sup(b) bound to the self-peptide dEV8 (EQYKFYSV) (B24) . We also briefly describe the 2.3 angstrom structure of H-2K.sup(b)-dEV8, which, along with the unliganded 2.5 angstrom structure of the 2C TCR (B15) , allows us to assess whether there are structural alterations in either the TCR or pMHC upon complexation. We can now more clearly explain the degenerate specificity of TCR-pMHC interaction in terms of a structural plasticity in the TCR-pMHC interface. The ability to alter the shape of the TCR combining site through deformation of the peptide-contacting complementarity-determining region (CDR) loops and their side chain orientations, along with large unfilled spaces in the interface, permits useful accommodation of different ligands. This in turn gives rise to the biological and functional plasticity that is based on varying affinities and stabilities observed in most TCR systems in the in vivo signal transduction events.

Overall structure. The 2C TCR and H-2K.sup(b)-dEV8 were expressed and

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Display 9/9/1 (Item 1 from file: 370)
DIALOG(R)File 370:Science

purified from Drosophila melanogaster cells and cocrystallized (B23) . The structure was determined by molecular replacement and refined with the use of multidomain real-space averaging and torsion angle dynamics (B25) (Table 1). The diffraction of these crystals is markedly anisotropic along the b* direction, thus limiting the effective resolution of the refined structure (maximum resolution along a* and c* is beyond 3.0 angstrom , but only ~4.2 angstrom along b*). Despite the presence of this anisotropic decay, all of the domains of the two TCR-pMHC complexes in the asymmetric unit are ordered (B26) , with the highest quality electron density being in the TCR-pMHC interfaces. The relation of the two molecules in the asymmetric unit (B27) does not support other crystallographically derived dimerization models for TCR-pMHC complexes (B28) .

The overall relative orientations of the TCR and pMHC in the refined 2C-H-2K.sup(b)-dEV8 complex are identical to those derived from the original molecular replacement solution (B15) . The TCR crosses the pMHC in an approximate diagonal orientation, in which the TCR a chain lies over the bound peptide NH.inf(2)-terminal residues and the (beta) chain covers the

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DIALOG(R)File 370:Science

peptide COOH-terminal residues (Figs. 1 and 2). Given the steric limitations that the MHC helices place on the depth of the approach of the TCR to the bound peptide, the diagonal orientation allows for the deepest docking solution of the TCR CDRs onto the pMHC surface. The unusual noncanonical fold of the TCR C.inf(a) domain (B15) is confirmed in each of the two complexes.

The TCR-pMHC interface. About 1876 angstrom .sup(2) of surface is buried in the 2C-K.sup(b) interface, of which 900 angstrom .sup(2) is contributed by the TCR and 976 angstrom .sup(2) by the pMHC (B25) . Within the pMHC composite surface, about 222 angstrom .sup(2), or 23% of the total, constitutes the bound dEV8 peptide, and 754 angstrom .sup(2) (77%) the buried surface from the MHC a helices. The small fraction of surface contributed by the peptide is a reflection of its deeply buried location within K.sup(b) molecules, which limits the amount of exposed surface area, as originally proposed in the H-2K.sup(b)-VSV and H-2K.sup(b)-SEV structures (B29) . In the A6-HLA-A2-Tax complex (B16) , the total buried surface area in the interface is similar (B30) , but the peptide fraction

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is greater (33%).

All of the 2C TCR CDRs contribute to the buried surface area in the interface (Fig. 1), contrary to the situation seen in the structure of the human A6 TCR in complex with HLA-A2-Tax (B30) , where (beta) chain CDRs 1 and 2 make essentially no contributions (B16) . For 2C, slightly more surface is buried by the a chain (470 angstrom .sup(2)) than the (beta) chain (430 angstrom .sup(2)), but within each chain the distribution of buried surface area by the CDRs varies: CDR1.inf(a), 214 angstrom .sup(2); CDR2.inf(a), 110 angstrom .sup(2); CDR3.inf(a), 140 angstrom .sup(2); CDR1.inf((beta)), 160 angstrom .sup(2); CDR2.inf((beta)), 167 angstrom .sup(2); CDR3.inf((beta)), 89 angstrom .sup(2); and HV4, 10 angstrom .sup(2). CDR3.inf((beta)) contributes the least buried surface of all the CDRs and is positioned over a largely empty pocket in the interface (Fig. 1). The overall contact surface is formed from 21 TCR, 16 MHC, and 5 peptide residues (Table 2).

TCR contacts with the MHC helices. Of the ~41 total intermolecular contacts between the TCR and pMHC, 27 are derived from CDR contacts with

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highly conserved MHC a1 and a2 a-helical residues (Table 2). CDRs 2.inf(a) and 2.inf((beta)) lie directly on top of the a2 and a1 helices, respectively, and, therefore, interact exclusively with the MHC (Fig. 2). CDRs 1.inf(a) and 1.inf((beta)) lie between the helices and are thus able to contact both peptide and MHC simultaneously. As originally speculated (B15) , the paucity of bulky side chains at the apices of CDRs 2 and 3 in both chains (Fig. 2A) allows the 2C TCR to approach the MHC heavy chain so as to maximize main chain van der Waals contacts and to position the two CDR3s to "read-out" the contents of the peptide binding groove. The predominant interaction of the TCR with the MHC helices in this complex, as also observed in the A6-HLA-A2-Tax complex (B16) , provides structural confirmation of long-standing hypotheses that the TCR repertoire must have evolved primarily with reactivity toward conserved features of the MHC heavy chain so that the most diverse portions of the receptor can discriminate among antigenic peptides (B17) (B18) (B19) .

A number of contacts (Table 2) at the periphery of the interface between the MHC helices and CDRs 1 and 2 appear to be between highly

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conserved residues and may play a key role in dictating (or steering) a generalized orientation. In particular, Ser.sup(27).sup(a) of CDR1.inf(a), which hydrogen bonds to the conserved K.sup(b) residue Glu.sup(58) (Fig. 3 A), and Ser.sup(51).sup(a) of CDR2.inf(a) [contacts Glu.sup(166) (Fig. 3A)] are the most frequently occurring residues to occur in V.inf(a) gene sequences at these positions (B31) . These interactions between conserved residues are consistent with recent data indicating a critical role for V.inf(a) residues 27.inf(a) and 51.inf(a) in the restriction of particular murine TCRs (V.inf(a)3.1 and V.inf(a)3.2) for MHC class I versus class II (B32) . In class II MHC molecules, the approximate corresponding residues of the class I H-2K.sup(b) Glu.sup(58) and Glu.sup(166) are different but still highly conserved (B33) . Other potentially conserved contacts appear

between a (Tyr.sup(31).sup(a)) and (beta) (His.sup(29).sup((beta)), Glu.sup(56).sup((beta))) chain residues to the MHC helices (Table 2).

Overall, the V.inf(a) CDR1 and CDR2 contact residues appear to be more highly conserved not only within K.sup(b)-restricted TCRs but also across other TCRs compared with the corresponding (beta) chain contact residues.

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In the A6-HLA-A2-Tax crystal structure, the A6 TCR V.inf(a) has a similar overall orientation as V.inf(a) in our complex, but it has minimal contact between the (beta) chain CDRs 1 and 2 and the pMHC. These similarities and differences would strongly infer that it is the a chain that dictates the orientation of that complex (discussed below).

A conserved framework for TCR binding to the MHC helices, or a generalized orientation, would enhance the flexibility in pMHC recognition by providing a scaffold in which the centrally located peptide can be finely sampled by the TCR (B18) . A large, conserved buried surface of relatively low affinity would facilitate short-lived complex formation by the TCR and MHC and subsequent "scanning" of the peptide (B34) .

A naturally occurring mutant of H-2K.sup(b), termed H-2K.sup(bm3) (Asp.sup(77) to Ser, Lys.sup(89) to Ala), is an alloreactive ligand for, and negatively selects, the 2C TCR (B21) . When bound to dEV8, H-2K.sup(bm3) generates a strong 2C cytotoxic T cell response (B6) . Of the two mutations in H-2K.sup(bm3), Asp.sup(77) to Ser has been identified as the one that causes the alloreactive response (B21) . In the

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2C-H-2K.sup(b)-dEV8 structure, Asp.sup(77) lies underneath CDR2.inf((beta)) but does not contact 2C; instead, it forms a hydrogen bond to the main chain of the P8 peptide residue. Replacement of Asp.sup(77) with Ser could disrupt this peptide contact and potentially alter the position of the peptide residues in contact with the TCR (especially Ser.sup(P7)) and also the conformation of the COOH-terminal region of the a1 helix, which is in contact with CDR2.inf((beta)). Additionally, removal of the Asp.sup(77) negative charge would alter the electrostatics of this patch of pMHC surface, which is buried by the TCR (B35) . Hence, even though Asp.sup(77) is not in direct contact with the TCR, its removal would clearly cause structural and electrostatic changes perceptible to 2C and lead to an alloreactive response.

TCR contact with bound peptide. The dEV8 peptide (EQYKFYSV) (B24) runs from CDR1.inf(a) to CDR1.inf((beta)) diagonally across the TCR surface between CDRs 3.inf(a) and 3.inf((beta)) (Fig. 2B), which lie primarily within the peptide binding groove between the a helices (Fig. 2D). The TCR interaction with the peptide is mediated directly and

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indirectly by hydrogen bonds to the functional groups of the upward-facing side chains (P1, P4, P6, and P7) from CDRs 1.inf(a), 1.inf((beta)), 3.inf(a), and 3.inf((beta)), which are in simultaneous contact with the a1 and a2 helices of the MHC (Figs. 1 and 2). The large hydrophobic central cavity between CDRs 3.inf(a) and 3.inf((beta)) remains unfilled, contrary to our previous expectations (B15) ; CDR3.inf((beta)) appears to have only a very limited interaction with the peptide at residue Tyr.sup(P6)

through a single contact with Gly.sup(97).sup((beta)) (Fig. 3B). Thus, CDR3.inf((beta)), which has been implicated in playing a primary role in peptide recognition in other TCRs (B16) (B36) , has negligible direct contact with the dEV8 peptide in our complex.

Overall, the interface between the TCR and pMHC exhibits poor shape complementarity (B37) , large empty spaces, and precarious peptide contacts, which is consistent with the weak affinity of this complex (dissociation constant, K.inf(D), of ~10.sup(-5)M) (B23) . The TCR interaction with the bound peptide antigen is through only the distal tips of the up-facing side chains, which are required to be completely extended

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in order to reach the TCR, even when water molecules are used as a bridge (Fig. 3A and Table 2). There appears to be sufficient space between the peptide and TCR to accommodate a wide range of different peptide residues, such as in the highly reactive synthetic peptide complex H-2K.sup(b)-SIYR (SIYRYYGL) (B24) (B38) , which contains different residues at the up-pointing P1, P4, and P7 positions, and in the 2C alloreactive ligand H-2L.sup(d)-p2Ca (B22) , where the upward-facing positions of the p2Ca peptide contain Pro, Phe, and Asp residues (B35) .

The poor complementarity of this self peptide-TCR interface is consistent with data that suggest self peptides involved in thymic positive selection may not have exquisite specificity for a particular TCR (B39) but instead cross-react with many TCRs. dEV8 is probably one of a degenerate set of peptides that positively select 2C (B6) , so its precarious contacts with 2C are consistent with this promiscuous role.

The 2C-H-2K.sup(b)-dEV8 complex also suggests the possibility of structural limitations to achieving significantly higher TCR -pMHC affinities than those within the range selected for during

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thymic maturation. The total buried surface area and the number of intermolecular interactions is similar to those found in high-affinity interfaces between proteins (B40) , but the shape complementarity in the center of this interface, between TCR and peptide, is extremely poor (B37) . In both 2C-H-2K.sup(b)-dEV8 and the A6-HLA-A2-Tax complex (B16) , which also exhibits poor shape complementarity (B37) , the peptide surface is effectively "held away" from the TCR combining site surface by the MHC a helices, thus severely limiting the intimacy of this contact.

That the CDRs simultaneously contact MHC helical residues and peptide antigen bears on the issue of a bias in V-region subtypes toward particular antigens (B41) . In the 2C-K.sup(b) structure, the bound peptide contacts both V (CDRs 1 and 3) and J (CDR3) segments of the V.inf(a), and V (CDR1) and D (CDR3) segments of the (beta) chain (Table 2). Contacts of the V region with the bound peptide by both a and (beta) chains would skew the chain distribution toward sequences that can satisfy the dual requirements of recognition of both MHC helices (either conserved or polymorphic positions on the a1 and a2 helices) and peptide side chains (B18) (B42) .

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Comparison of liganded and unliganded TCR and pMHC. Comparison of the complex structure with the 2.5 angstrom unliganded 2C structure (B15)

and the 2.3 angstrom crystal structure of H-2K.sup(b)-dEV8, which we only briefly describe here, has enabled us to identify large structural rearrangements that significantly affect the TCR-pMHC interaction. For 2C, the liganded and unliganded TCRs superimpose closely, showing no major domain rearrangements (B26) (B43) . However, large accommodative movements have occurred in the three CDRs that are most intimately associated with peptide (Fig. 4 A). The magnitude of these changes are large when compared with those seen so far in protein-antibody complexes (B44) . CDR1.inf(a) has undergone a hinge movement of ~4.2 angstrom between residues 25.inf(a) and 29.inf(a) to avoid collision with the MHC a1 helix (Fig. 4A). CDR3.inf(a) residues 99.inf(a) to 102.inf(a) [3.2 angstrom root mean square deviation (rmsd)] have undergone the largest conformational change of all the CDRs. In the unliganded 2C, this CDR has a type II (prime) (beta) turn, with Phe.sup(100).sup(a) protruding from the tip [see figure 8A in (B15)]. In the complex, it is instead bent back by 6 angstrom so

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that the tip of the CDR interacts with the MHC a2 helix (Figs. 3B and 4A). The conformation of CDR3.inf((beta)) is similar to that in the unliganded structure, with the exception of a small segmental shift (~1 to 2 angstrom) (Fig. 4A), which is consistent with its minimal direct contact with the pMHC surface (Table 2). The lack of movement of the other CDRs that primarily contact the MHC a helices is consistent with their involvement in conserved interactions (Fig. 4A).

These large conformational adjustments to the pMHC (Fig. 4A), especially for the peptide-contacting CDRs, is an additional mechanism of enhancing the TCR recognition repertoire and accommodating multiple peptide ligands. In antibodies, large CDR conformational changes, particularly in CDR-H3, have been documented upon antigen binding, particularly with peptides and small molecules (B45) . Analogous to the TCR, which does not undergo affinity maturation, germline antibodies have been seen to utilize conformational change as a means of compensating for nonoptimal complementarity to their antigen (B46) . However, the major conformational changes in the TCR are localized to the combining site and do not appear to

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